Please substitute the following paragraph for the first paragraph starting on page 1 of the specification.

Page 1, paragraph 1 (Currently Amended)

This application is the National Phase filing of International Patent Application No. PCT/JP2004/001181, filed February ~~2,~~ 5, 2004.

Please substitute the following paragraph for the first paragraph starting on page 3 of the specification.

Page 3, paragraph 1 (Currently Amended)

The present invention is to provide a new ~~bicyclic~~ compound that is useful for preventing and treating HIV infection, especially AIDS, due to its CCR antagonist activity, especially CCR5 antagonist activity.

Please substitute the following paragraph for the second paragraph starting on page 13 of the specification.

Page 13, paragraph 2 (Currently Amended)

In the above-described formula (I), the "5- or 6-membered ring" in the "5- or 6-membered ring ~~group~~ which may be substituted" represented by R^1 may be exemplified by a group which is formed by eliminating a hydrogen atom from 6-membered aromatic hydrocarbon such as benzene, etc.; 5- or 6-membered aliphatic hydrocarbon such as cyclopentane, cyclohexane, cyclopentene, cyclohexene, ~~cyclopentanediene,~~ cyclopentadiene, ~~cyclohexanediene,~~ cyclohexadiene, etc.; 5- or 6-membered aromatic heterocycle containing 1 to 4 heteroatoms of one or two kinds selected from nitrogen, sulfur and oxygen atoms, such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- or 6-membered non-aromatic heterocycle

containing 1 to 4 heteroatoms of one or two kinds selected from nitrogen, sulfur and oxygen atoms, such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran, etc.; or the like. Among them, the "5- or 6-membered ring" is preferably benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran (preferably, 6-membered ring), or the like, it being particularly preferably benzene.

Please substitute the following paragraph for the second paragraph starting on page 14 of the specification.

Page 14, paragraph 2 (Currently Amended)

The substituent which may be carried by the "5- or 6-membered ring" of the "5- or 6-membered ring ~~group~~ which may be substituted" represented by R^1 may be exemplified by halogen atom, nitro, cyano, alkyl which may be substituted, cycloalkyl which may be substituted, hydroxy group which may be substituted, thiol group which may be substituted (wherein the sulfur atom may be oxidized, and may form sulfinyl which may be substituted or sulfonyl which may be substituted), amino group which may be substituted, acyl which may be substituted, carboxyl group which may be esterified, an aromatic group which may be substituted, or the like.

Please substitute the following paragraph for the second paragraph starting on page 29 of the specification.

Page 29, paragraph 2 (Currently Amended)

The number of the above substituents of R^1 may be 1 to 4, preferably 1 to 2, and the substituents which may be identical with or different from each other may be present at any possible positions of the ring. When the "5- or 6-membered ring" of the "5- to 6-membered ring which may be substituted" represented by R^1 has two or more substituents, two of the substituents may be bonded to each other to form, for example, lower (C_{1-6}) alkylene (for example, trimethylene, tetramethylene, etc.), lower (C_{1-6}) alkyleneoxy (for example, $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-$, $-O-CH_2-CH_2-CH_2-CH_2-$, $-O-C(CH_3)(CH_3)-CH_2-CH_2-$, etc.), lower ($C_{1-6}$) alkylenethio (for example, $-CH_2-S-CH_2-$, $-S-CH_2-CH_2-$, $-S-CH_2-CH_2-CH_2-$, $-S-CH_2-CH_2-CH_2-CH_2-$, $-S-C(CH_3)(CH_3)-CH_2-CH_2-$, etc.), lower ($C_{1-6}$) alkylenedioxy (for example, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-O-CH_2-CH_2-CH_2-O-$, etc.), lower (C_{1-6}) alkylenedithio (for example, $-S-CH_2-S-$, $-S-CH_2-CH_2-S-$, $-S-CH_2-CH_2-CH_2-S-$, etc.), oxy-lower (C_{1-6}) alkyleneamino (for example, $-O-CH_2-NH-$, $-O-CH_2-CH_2-NH-$, etc.), oxy-lower (C_{1-6}) alkylenethio (for example, $-O-CH_2-S-$, $-O-CH_2-CH_2-S-$, etc.), lower (C_{1-6}) alkyleneamino (for example, $-NH-CH_2-CH_2-$, $-NH-CH_2-CH_2-CH_2-$, etc.), lower (C_{1-6}) alkylenediamino (for example, $-NH-CH_2-NH-$, $-NH-CH_2-CH_2-NH-$, etc.), ~~thialower~~ **thiolower** (C_{1-6}) alkyleneamino (for example, $-S-CH_2-NH-$, $-S-CH_2-CH_2-NH-$, etc.), lower (C_{2-6}) alkenylene (for example, $-CH_2-CH=CH-$, $-CH_2-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, etc.), lower (C_{4-6}) alkadienylene (for example, $-CH=CH-CH=CH-$, etc.), and the like.

Please substitute the following paragraph for the second paragraph starting on page 31 of the specification.

Page 31, paragraph 2 (Currently Amended)

The "substituent" of the "5- or 6-membered ring" of the "5- or 6-membered ring ~~group~~ which may be substituted" represented by R^1 may be exemplified by, in particular, lower (C_{1-4}) alkyl which may be halogenated or lower (C_{1-4}) alkoxylated (for example, methyl, ethyl, t-butyl, trifluoromethyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, methoxyethyl, ethoxylethyl, propoxyethyl, butoxyethyl, etc.), lower (C_{1-4}) alkoxy which may be halogenated or lower (C_{1-4}) alkoxylated (for example, methoxy, ethoxy, propoxy, butoxy, t-butoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, methoxyethoxy, ethoxyethoxy, propoxyethoxy, butoxyethoxy, methoxypropoxy, ethoxypropoxy, propoxypropoxy, butoxypropoxy, etc.), halogen (for example, fluorine, chlorine, etc.), nitro, cyano, amino which may be substituted with one or two of lower (C_{1-4}) alkyl, formyl or lower (C_{2-4}) alkanoyl (for example, amino, methylamino, dimethylamino, formylamino, acetylamino, etc.), 5- or 6-membered cycloamino (for example, 1-pyrrolidinyl, 1-piperazinyl, 1-piperidinyl, 4-morpholino, 4-thiomorpholino, 1-imidazolyl, 4-tetrahydropyranyl, etc.), or the like.

Please substitute the following paragraph for the second paragraph starting on page 43 of the specification.

Page 43, paragraph 2 (Currently Amended)

The "5- or 6-membered aromatic ring which may be substituted" represented by Z^1 may have the same substituent as the "substituent" which may be carried by the "5- or 6-membered ring" of the "5- or 6-membered ring which may be substituted" represented by R^1, and among the substituents, a halogen atom (for example, fluorine, chlorine, bromine, etc.), a C_{1-4} alkyl group

which may be substituted with halogen atom(s) (for example, methyl, ethyl, ~~trifiluoromethyl,~~ **trifluoromethyl,** trifluoroethyl, etc.), a C_{1-4} alkoxy group which may be substituted with halogen atom(s) (for example, methoxy, ethoxy, propoxy, trifluoromethoxy, trifluoroethoxy, etc.) and the like are preferred. However, it is preferred that there is no other substituent than X^2 and Z^2, and it is preferred that when Z^1 is a 6-membered ring (preferably benzene), the position of substitution of Z^2 is para to X^2. Further, for the substituent of Z^1, benzene which may be substituted with 1) a halogen atom, 2) a C_{1-4} alkyl group which may be substituted with halogen atom(s), or 3) a C_{1-4} alkoxy group which may be substituted with halogen atom(s) is preferred, and in particular, benzene which may be substituted with methyl or trifluoromethyl is preferred.

Please substitute the following paragraph for the first paragraph starting on page 45 of the specification.

Page 45, paragraph 1 (Currently Amended)

The alkylene chain of the "alkylene ~~group~~ **chain** which may be substituted" represented by W^1 and W^2 may be exemplified by the alkylene chain represented by $-(CH_2)_{k1}-$ (wherein k1 is an integer of 1 to 4) or the like. The alkenylene ~~group~~ **chain** of the "alkenylene ~~group~~ **chain** which may be substituted" represented by W^1 may be exemplified by the alkenylene chain represented by $-(CH_2)_{k2}-(CH=CH)-(CH_2)_{k3}-$ (wherein k2 and k3 are identical or different, and represent 0, 1 or 2, respectively, provided that the sum of k2 and k3 is 2 or less) or the like. The alkylene ~~group~~ **chain** and alkenylene ~~group~~ **chain** represented by said W^1 and W^2 may be substituted at any arbitrary position (preferably on a carbon atom), and such substituent may be any substituent capable of bonding to the alkylene chain or alkenylene chain which constitutes the straight chain moiety. Examples thereof include lower (C_{1-6}) alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl,

etc.), lower (C_{3-7})cycloalkyl (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.), formyl, lower (C_{2-7}) alkanoyl, (for example, acetyl, propionyl, butyryl, etc.), phosphono which may be esterified, carboxyl which may be esterified or amidated, hydroxy group, oxo, hydroxyimino group, lower (C_{1-6}) alkoxyimino group which may be substituted, and the like, and preferably lower alkyl having 1 to 6 carbon atoms (preferably, C_{1-3} alkyl), hydroxy group, oxo, hydroxyimino group, lower (C_{1-6}) alkoxyimino group (which may be substituted with a polar group such as hydroxy group, cyano group, carboxyl group which may be esterified or amidated (for example, carboxyl, C_{1-4} alkoxycarbonyl, carbamoyl, mono-C_{1-4} alkylcarbamoyl, di-C_{1-4} alkylcarbamoyl, etc.), etc.) or the like.

Please substitute the following paragraph for the second paragraph starting on page 46 of the specification.

Page 46, paragraph 2 (Currently Amended)

The phosphono group which may be esterified may be exemplified by a group represented by $P(O)(OR^{12})(OR^{13})$, wherein R^{12} and R^{13} are each hydrogen, an alkyl group having 1 to 6 carbon atoms, or a cycloalkyl group having 3 to 7 carbon atoms, or R^{12} and ~~R^{10}~~ $\underline{R^{13}}$ may be bonded to each other to form a 5- to 7-membered ring.

Please substitute the following paragraph for the third paragraph on page 49 of the specification.

Page 49, paragraph 3 (Currently Amended)

(1) alkyl which may be substituted (for example, C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., and preferably lower (C_{1-6}) alkyl, or the like); and

Please substitute the following paragraph for the fourth paragraph on page 49 of the specification.

Page 49, paragraph 4 (Currently Amended)

(2) cycloalkyl which may be substituted (for example, C_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, ~~cyanooctyl,~~ **cyclooctyl,** etc., or the like);

Please substitute the following paragraph for the second paragraph on page 50 of the specification.

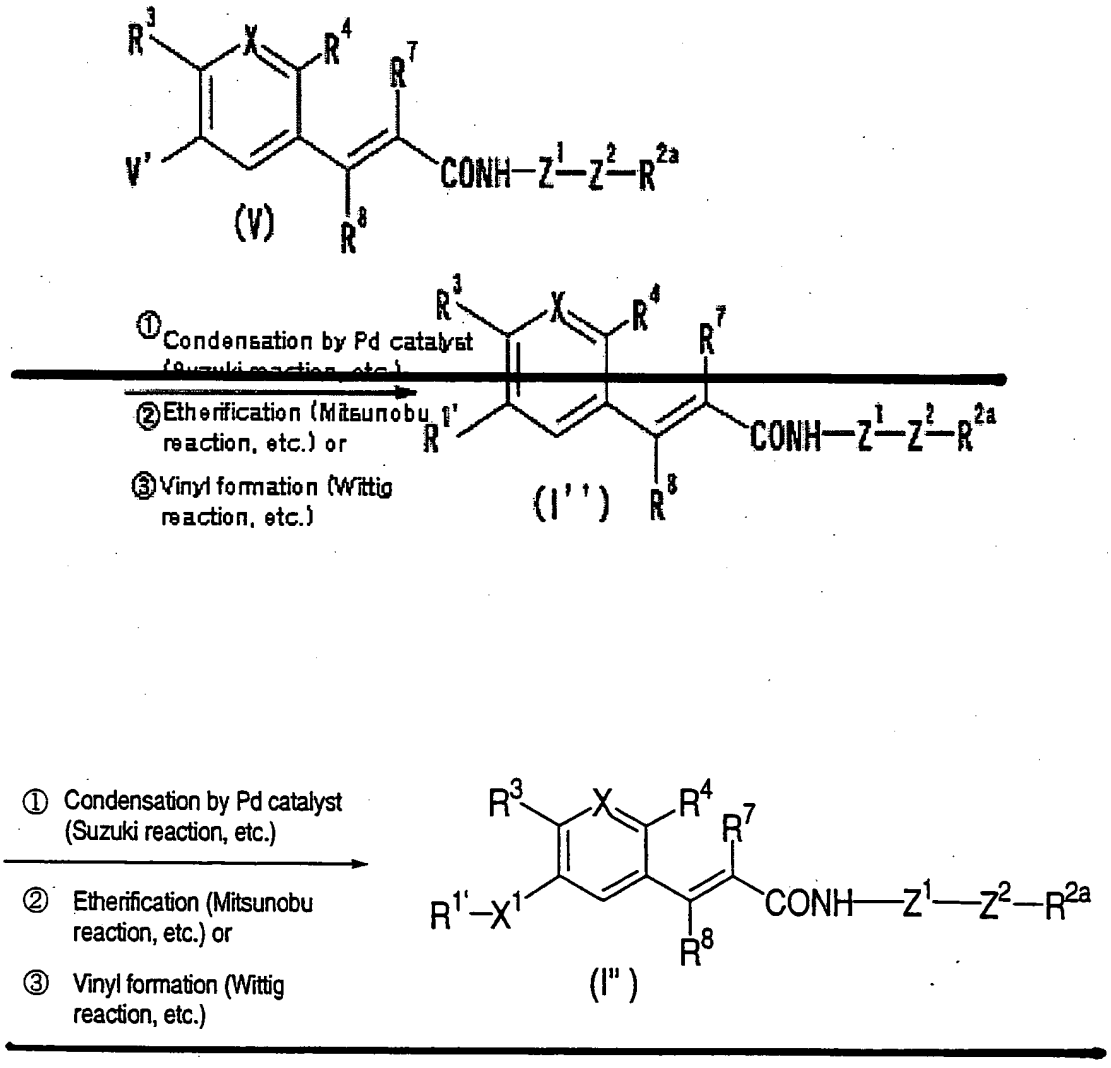
Page 50, paragraph 2 (Currently Amended)

(2-1) the cycloalkyl may contain one heteroatom selected from sulfur, oxygen and nitrogen atoms, forming oxirane, thiolane, aziridine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, tetrahydrothiopyran, ~~tetrahydrothiopyran~~ **tetrahydrothiopyran-**1-oxide, piperidine, etc. (preferably, a 6-membered ring such as tetrahydropyran, tetrahydrothiopyran, piperidine, etc.), and the bond with the amino group is preferably present at the 3- or 4-position (preferably, at the 4-position);

Please substitute the following paragraph for the second paragraph on page 90 of the specification.

Page 90, paragraph 2 (Currently Amended)

[Process D]



(1) Compound (V), wherein V' represents a halogen atom (bromine, iodine, etc.) or a sulfonyloxy group (trifluoromethanesulfonyloxy group, etc), and the other symbols have the same meanings as described above, can ~~besubjected~~ **be subjected** to, for example, the Suzuki

reaction [a cross-~~condensation~~ **coupling** reaction of an arylboric acid and, for example, an aryl halide or aryloxytrifluoromethanesulfonate, catalyzed by a palladium catalyst; A. Suzuki et al., Synth. Commun., 11, 513 (1981)], to prepare a Compound (I") in which X^1 is a bond, and $R^{1'}$ is a 5- or 6-membered aromatic group. The aryl borate can be used in an amount of about an equivalent to 1.5-fold moles with respect to 1 mole of Compound (V) to give Compound (I").

Please substitute the following paragraph for the second paragraph on page 91 of the specification.

Page 91, paragraph 2 (Currently Amended)

Further, Compound (V) can be subjected to, for example, a cross-~~condensation~~ **coupling** reaction with an arylacetylene compound in the presence of a palladium catalyst [dichlorobis(triphenylphosphine)palladium, etc.] [K.S.Y. Lau et al., J. Org. Chem., 46, 2280 (1981); J.W. Tilley, S. Zawoisky et al., J, Org. Chem., 53, 386 (1988)] to give a Compound (I") having an acetylene bond, in which X^1 represents -C≡C-. The arylacetylene compound can be used typically in an amount of about an equivalent to two-fold moles with respect to 1 mole of Compound (V) to prepare Compound (I").

Please substitute the following paragraph for the third paragraph on page 100 of the specification.

Page 100, paragraph 3 (Currently Amended)

The compound represented by formula (I) of the present invention or a salt thereof including the above-mentioned Compound (I-1), Compound (I-2), Compound (I'), Compound (I'') and Compound (I''') (hereinafter, when it is said "the compound represented by formula (I)" in brief, it means to include ~~a salt thereof and~~ the compound represented by formula (I) and a

salt thereof) can be administered orally or parenterally alone or by as a pharmaceutical composition comprising the compound mixed with a pharmaceutically acceptable carrier in the form of a solid preparation such as tablet, capsule, granule, powder, etc., or a liquid preparation such as syrup, injectable solution, etc.

Please substitute the following paragraph for the second paragraph on page 108 of the specification.

Page 108, paragraph 2 (Currently Amended)

The pharmaceutical composition containing the compound represented by formula (I) or a salt thereof may vary depending on the kind of disease to be treated and may be used in combination with other drugs. Examples of the other drugs include HDL-increasing drugs [squalene synthase inhibitor, CETP inhibitor, LPL activator, etc.]; prophylactic and/or therapeutic agents for HIV infection [nucleic acid reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, adefovir, adefovir dipivoxil, fozivudine tidoxil, etc., non-nucleic acid reverse transcriptase inhibitors such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, etc., protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, palinavir, lasinavir, lopinavir, etc.]; ~~NMG-CoA~~ HMG-CoA reductase inhibitors [cerivastatin, atorvastatin, pravastatin, simvastatin, itavastatin, lovastatin, fluvastatin, (+)-3R,5S-7-[4-[4-fluorophenyl]-6-isopropyl-2-(N-methyl-N-methanesulfonylamino]pyrimidin-5-yl]-3,5-dihydroxy-6(E)-heptenoic acid, etc.]; atopic dermatitis drugs [sodium cromoglycate, etc.]; allergic nasal catarrh drugs [sodium cromoglycate, chlorpheniramine maleate, alimemazine tartrate, clemastine fumarate, homochlorcyclizine hydrochloride, terfenadine, mequitazine, etc.]; imipenem·cilastatin sodium; endotoxin antagonists or antibodies; oxidosqualene-lanosterol cyclases [e.g., decalin derivatives, azadecalin

derivatives and indane derivatives]; calcium antagonists (diltiazem, etc.); glycerol; cholinesterase inhibitors (e.g., Aricept (donepezil), etc.); compounds suppressing cholesterol uptake [e.g., sitosterol, neomycin, etc.]; compounds inhibiting cholesterol biosyntheses [e.g., HMG-CoA reductase inhibitors such as lovastatin, simvastatin, pravastatin, etc.];

Please substitute the following paragraph for the second paragraph on page 110 of the specification.

Page 110, paragraph 2 (Currently Amended)

cyclooxygenase inhibitors [Cox-I, Cox-II inhibitors such as celecoxib, rofecoxib, salicylic acid derivatives such as aspirin and the like, diclofenac, indometacin, loxoprofen, etc.]; signal transduction inhibitors, squalene epoxidase inhibitors [e.g., NB-598 and the analogous compounds, etc.]; steroidal drugs [dexamethasone, hexestrol, methimazole, betamethasone, triamcinolone, triamcinolone acetonide, fluocinonide, fluocinolone acetonide, prednisolone, methylprednisolone, cortisone acetate, hydrocortisone, fluorometholone, beclomethasone propionate, estriol, etc.]; diacerin; nicotinic acid and derivatives and analogues thereof [e.g., acipimox and probucol]; nicergoline, nephrotic syndrome drugs: prednisolone (Predonine), prednisolone sodium succinate (Predonine), methylprednisolone sodium succinate (Solumedrol), betamethasone (Rinderon), dipyridamole (Persantine), dilazep hydrochloride (Comelian), ticlopidine, clopidogrel, antiplatelet drugs and anticoagulants such as FXa inhibitors, etc.; ~~barpital-based~~ **barbital-based** anticonvulsants or anaesthetic drugs (phenobarbital, mephobarbital, metharbital, etc.); Parkinson's disease drugs (e.g., L-DOPA, etc.); histamine receptor blockers (cimetidine, famotidine, etc.); hydantoin-based anticonvulsant drugs (phenytoin, mephenytoin, ethotoin, etc.); piroxicam, fibrates [e.g., clofibrate, benzafibrate, gemfibrozil, etc.]; prostaglandins; megestrol acetate; gastric and intraduodenal ulcer drugs:

antacids [e.g., histamine H2 antagonists (cimetidine, etc.), proton pump inhibitors (lansoprazole, etc.), etc.]; inflammatory mediator inhibitors; coronary vasodilators: nifedipine, diltiazem, ~~nicoradil,~~ **nicorandil,** nitrite drugs, etc.; infectious disease drugs: [e.g., antibiotic formulations (cefotiam hydrochloride, cefozopran hydrochloride, ampicillin, etc.), chemotherapeutic agents (sulfa drugs, synthetic antibacterial agents, antiviral agents, etc.), biological formulations (vaccines, blood preparations including immunoglobulins) etc.] etc.; hepatic disease drugs: glycyrrhizin formulations [e.g., Stronger Minophagen, etc.]; liver hydrolysate; SH compounds [e.g., glutathione, etc.]; special amino acid formulations [e.g., aminoleban, etc.]; phospholipids [e.g., polyene-phosphatidylcholine, etc.]; vitamins [e.g., vitamin B_1, B_2, B_6, B_{12}, C, etc.]; adrenocortical hormones [e.g., dexamethasone, betamethasone, etc.]; interferons [e.g., interferon α, β, etc.]; hepatic encephalopathy drugs [e.g., lactulose, etc.];

Please substitute the following paragraph for the second paragraph on page 111 of the specification.

Page 111, paragraph 2 (Currently Amended)

hemostatic agents used in cases of rupture of esophageal and gastric varices [e.g., vasopressin, somatostatin, etc.] etc.; arthritis drugs; muscle relaxants [pridinol, tubocurarine, pancuronium, tolperisone hydrochloride, chlorphenesin carbamate, baclofen, chlormezanone, mephenesin, chlorzoxazone, eperisone, tizanidine, etc.]; vasodilators [oxyfedrine, diltiazem, tolazoline, hexobendine, bamethan, clonidine, methyldopa, guanabenz, etc.]; vasoconstrictors [dopamine, dobutamine, denopamine, etc.]; platelet coagulation inhibitors (ozagrel, etc.); thrombogenesis prophylactic and/or therapeutic drugs: anticoagulant drugs [e.g., heparin sodium, heparin calcium, warfarin calcium (Warfarin), Xa inhibitor]; thrombolytic drugs [e.g., tPA, urokinase]; antiplatelet drugs [e.g., aspirin, sulfinpyrazone (Anturan), dipyridamole (Persantine),

ticlopidine (Panaldine), cilostazol (Pletal), GPIIb/IIIa antagonists (ReoPro)]; antidepressants [imipramine, clomipramine, noxiptiline, fenelzin, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, mianserin hydrochloride, maprotiline hydrochloride, sulpiride, fluvoxamine maleate, trazodone hydrochloride, etc.]; antiepileptic drugs [gabapentin, phenytoin, ethosuximide, acetazolamide, chlordiazepoxide, trimethadione, carbamazepine, phenobarbital, primidone, sultiame, sodium valproate, clonazepam, diazepam, nitrazepam, etc.]; antiallergic drugs [diphenhydramine, chlorpheniramine, tripelennamine, ~~methodilamine,~~ **methdilazine,** clemizole, diphenylpyraline, methoxyphenamine, sodium cromoglycate, tranilast, repirinast, amlexanox, ibudilast, ketotifen, terfenadine, mequitazine, azalastine, epinastine, ozagrel hydrochloride, pranlukast hydrate, seratrodast, fexofenadine, ebastine, bucillamine, oxatomide, Stronger Neo-Minophagen C, tranexamic acid, ketotifen fumarate, etc.]; anticholinergic drugs (e.g., ipratropium bromide, flutropium bromide, oxitropium bromide, etc.); anti-Parkinson drugs (dopamine, levodopa, etc.); antirheumatic drugs; anti-inflammatory drugs (e.g., aspirin, acetaminophen, diclofenac sodium, ibuprofen, indometacin, loxoprofen sodium, dexamethasone, etc.); anticoagulant and antiplatelet drugs [sodium citrate, activated protein C, tissue factor pathway inhibitors, antithrombin III, dalteparin sodium, argatroban, gabexate, ozagrel sodium, ethyl icosapentate, beraprost sodium, alprostadil, pentoxifylline, tisokinase, streptokinase, ~~hebarin,~~ **heparin,** etc.]; anticoagulant therapeutic drugs [dipyridamole ~~(Bersantine),~~ **(Persantine),** dilazep hydrochloride (Comelian), ticlopidine, clopidogrel, Xa inhibitors]; antibacterial drugs [(1) sulfa drugs [sulfamethizole, sulfisoxazole, sulfamonomethoxine, sulfamethizole, salazosulfapyridine, sulfadiazine silver, etc.], (2) ~~quinoline-based~~ **quinolone-based** antibacterial drugs [nalidixic acid, pipemidic acid trihydrate, enoxacin, norfloxacin, ofloxacin, tosufloxacin tosilate, ciprofloxacin hydrochloride, lomefloxacin hydrochloride,

sparfloxacin, fleroxacin, etc.], (3) antituberculous drugs [isoniazid, ethambutol (ethambutol hydrochloride), p-aminosalicylic acid (calcium p-aminosalicylate), pyrazinamide, ethionamide, prothionamide, rifampicin, streptomycin sulfate, kanamycin sulfate, cycloserine, etc.], (4) anti-acid fast bacterial drugs [diaphenylsulfone, ~~**rifampicilin,**~~ **rifampicin,** etc.], (5) antiviral drugs [idoxuridine, acyclovir, vidarabine, ganciclovir, etc.], (6) anti-HIV drugs [zidovudine, didanosine, zalcitabine, indinavir sulfate ethanolate, ritonavir, etc.], (7) spirocheticide, (8) antibiotics [tetracycline hydrochloride, ampicillin, piperacillin, gentamicin, dibekacin, kanendomycin, lividomycin, tobramycin, amikacin, fradiomycin, sisomicin, tetracycline, oxytetracycline, rolitetracycline, doxycycline, ampicillin, piperacillin, ticarcillin, cephalothin, cephapirin, cephaloridine, cefaclor, cephalexin, cefroxadine, cefadroxil, cefamandole, cefotiam, cefuroxime, cefotiam, cefotiam hexetil, cefuroxime axetil, cefdinir, cefditoren pivoxil, ceftazidime, cefpiramide, cefsulodin, cefmenoxime, cefpodoxime proxetil, cefpirome, cefozopran, cefepime, cefsulodin, cefmetazole, cefminox, cefoxitin, cefbuperazone, latamoxef, flomoxef, cefazolin, cefotaxime, cefoperazone, ceftizoxime, moxalactam, thienamycin, sulfazecin, aztreonam or salts thereof, griseofulvin, lankacidins [J. Antibiotics, 38, 877-885 (1985)], etc.],

Please substitute the following paragraph for the second paragraph on page 116 of the specification.

Page 116, paragraph 2 (Currently Amended)

antiulcer drugs [metoclopramide, histidine hydrochloride, lansoprazole, metoclopramide, pirenzepine, cimetidine, ranitidine, famotidine, urogastron, oxethazaine, proglumide, omeprazole, sucralfate, sulpiride, cetraxate, gefarnate, aldioxa, teprenone, prostaglandins, etc.]; anti-diabetic drugs [e.g., pioglitazone, nateglinide, voglibose, acarbose, etc.]; antiobesity drugs

(mazindol, etc.); antirheumatic drugs, etc.; antianxiety drugs [diazepam, lorazepam, oxazepam, chlordiazepoxide, medazepam, oxazolam, cloxazolam, clotiazepam, bromazepam, etizolam, fludiazepam, hydroxyzine, etc.]; antiarrhythmic drugs : disopyramide, lidocaine, quinidine sulfate, flecainide acetate, mexiletine hydrochloride, amiodarone hydrochloride, and β blockers, Ca antagonists, etc.; antiasthmatic drugs [isoprenaline hydrochloride, salbutamol sulfate, procaterol hydrochloride, terbutaline sulfate, ~~**trimetoxynol**~~ **trimetoquinol** hydrochloride, tulobuterol hydrochloride, orciprenaline sulfate, fenoterol hydrobromide, ephedrine hydrochloride, ipratropium bromide, oxitropium bromide, flutropium bromide, theophylline, aminophylline, sodium cromoglycate, tranilast, repirinast, amlexanox, ibudilast, ketotifen, terfenadine, mequitazine, azelastine, epinastine, ozagrel hydrochloride, pranlukast hydrate, seratrodast, dexamethasone, prednisolone, hydrocortisone, beclomethasone propionate, fluticasone propionate, beclomethasone propionate, procaterol, etc.]; anti-hypothyroidism drugs [dried thyroid (Thyreoid), levothyroxine sodium (Thyradin S), liothyronine sodium (thyronine, tyronamine)]; nephrotic syndrome drugs [prednisolone (Predonine), prednisolone sodium succinate (Predonine), methylprednisolone sodium succinate (Solumedrol), betamethasone (Rinderon)]; antihypertensive drugs [(1) sympathetic nerve inhibitors [α2 stimulants (e.g., clonidine, guanabenz, guanfacine, methyldopa, etc.), ganglionic blockers (e.g., hexamethonium, trimethaphan, etc.), presynaptic blockers (e.g., ArsA-Oxylone, dimethylaminoreserpinate, rescinnamine, reserpine, syrosingopine, etc.), neuronal blockers (e.g., betanidine , guanethidine, etc.), α1 blockers (e.g., bunazosin, doxazosin, prazosin, terazosin, urapidil, etc.),

Please substitute the following paragraph for the second paragraph on page 117 of the specification.

Page 117, paragraph 2 (Currently Amended)

β blockers (e.g., propranolol, nadolol, timolol, nipradilol, bunitrolol, indenolol, penbutolol, carteolol, carvedilol, pindolol, acebutolol, atenolol, ~~pisoprolol,~~ **bisoprolol,** metoprolol, labetalol, amosulalol, arotinolol, etc.), etc.], (2) vasodilators [calcium channel antagonists (e.g., manidipine, nicardipine, nilvadipine, nisoldipine, nitrendipine, benidipine, amlodipine, aranidipine, etc.), phthalazine derivatives (e.g., budralazine, cadralazine, ecarazine, hydralazine, todralazine, etc.), etc.], (3) ACE inhibitors [alacepril, captopril, cilazapril, delapril, enalapril, lisinopril, temocapril, trandolapril, quinapril, imidapril, benazepril, perindopril, etc.)], (4) AII antagonists [losartan, candesartan, valsartan, telmisartan, irbesartan, forasartan, etc.], (5) diuretic drugs [e.g., diuretic drugs described above, etc.]; antihypertensive drugs: diuretic drugs [e.g., furosemide (Lasix), bumetanide (Lunetoron), azosemide (Diart)], antihypertensive drugs [e.g., ACE inhibitors, (enalapril maleate (Renivace), etc.) and Ca antagonists (manidipine, amlodipine, etc.), α or β receptor blockers, etc.], antihyperlipemia drugs [HMG-CoA reductase inhibitors (e.g., fluvastatin, cerivastatin, atorvastatin, etc.), fibrates [e.g., simfibrate, aluminum clofibrate, clinofibrate, fenofibrate, etc.], anion exchange resins (e.g., cholestyramine, etc.), nicotinic acid drugs (e.g., nicomol, niceritrol, tocopherol nicotinate etc.), polyvalent unsaturated fatty acid derivatives (e.g., ethyl icosapentate, polyene phosphatidylcholine, melinamide, etc.), phytosterols (e.g., gamma-oryzanol, soy sterol, etc.), elastase, sodium dextran sulfate, squalene synthase inhibitors, CETP inhibitors, ~~ethyl 2-chloro-3[4-(2-methyl-2-phenylpropoxy)phenyl]propionate~~ **ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate** [Chem. Pharm. Bull., 38, 2792-2796 (1990)], etc.]; osteopathic disease drugs: calcium formulations (e.g., calcium carbonate, etc.), calcitonin

formulations, activated vitamin D_3 formulations (e.g., alfacalcidol (Alfarol, etc.), calcitriol (Rocaltrol), etc.),

Please substitute the following paragraph for the second paragraph on page 119 of the specification.

Page 119, paragraph 2 (Currently Amended)

sex hormones (e.g., estrogen, ~~estrandiol,~~ **estradiol,** etc.), hormone formulations [e.g., conjugated estrogen (Premarin), etc.], ~~ibriflavone~~ **ipriflavone** formulations [Osten, etc.], vitamin K_2 , vitamin K_2 formulations [e.g., menatetrenone (Glakay), etc.], bisphosphonate-based formulations (etidronate, etc.), prostaglandin E2, fluorine compounds (e.g., sodium fluoride, etc.), bone morphogenetic protein (BMP), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factor (TGF-β), insulin-like growth factor-1 and -2 (IGF-1,-2), parathyroid adrenal hormones (PTH), and compounds described in EP-A1-376197, EP-A1-460488, and EP-A1-719782 (e.g., (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-benzothiepin-2-carboxamide, etc.), etc., fat-soluble vitamin drugs [(1) vitamin A family: vitamin A_1, vitamin A_2, and retinol palmitate, (2) vitamin D family: vitamin D_1, D_2, D_3, D_4 and D_5, (3) vitamin E family: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, dl-α-tocopherol nicotinate, (4) vitamin K family: vitamin K_1, K_2, K_3 and K_4, (5) folic acids (vitamin M, etc.); vitamin derivatives [various vitamin derivatives, e.g., vitamin D_3 derivatives such as 5,6-trans-cholecalciferol, 2,5-hydroxycholecalciferol, 1-α-hydroxycholecalciferol, vitamin D_2 derivatives such as 5,6-trans-ergocalciferol, and the like]; disease-modifying antirheumatic and immunosuppressive drugs [e.g., methotrexate, leflunomide, prograf, sulfasalazine, D-penicillamine, oral gold drugs];

hypertensors [dopamine, dobutamine, denopamine, digitoxin, digoxin, methyldigoxin, lanatoside C, G-strophanthin, etc.]; myocardial protective drugs: heart ATP-K opener, Na-H exchange inhibitors, endothelin antagonists, urotensin antagonist, etc., cardiac failure drugs [cardiac stimulants (e.g., digitoxin, digoxin, methyldigoxin, lanatoside C, proscillaridin, etc.), α, β stimulants (e.g., epinephrine, norepinephrine, isoproterenol, dopamine, docarpamine, dobutamine, denopamine, etc.), phosphodiesterase inhibitors (e.g., amrinone, milrinone, olprinone hydrochloride, etc.),

Please substitute the following paragraph for the second paragraph on page 120 of the specification.

Page 120, paragraph 2 (Currently Amended)

calcium channel sensitivity enhancers (e.g., ~~**pimobentan,**~~ **pimobendan,** etc.), nitrate drugs (e.g., nitroglycerin, isosorbide nitrate, etc.), ACE inhibitors (e.g., the ACE inhibitor described above, etc.), diuretic drugs (e.g., diuretic drugs described above, etc.), calperitide, ubidecarenone, vesnarinone, aminophylline, etc.]; neurotrophic factors; renal failure and nephropathy drugs; biological formulations [e.g., monoclonal antibodies (e.g., anti-TNF-α antibodies, anti-IL-12 antibodies, anti-IL-6 antibodies, anti-ICAM-I antibodies, anti-CD4 antibodies, etc.), soluble receptors (e.g., soluble TNF-α receptors, etc.), protein ligands (IL-I receptor antagonist, etc.)]; bile acid binding resins [e.g., cholestyramine, cholestipol, etc.]; biliary tract disease drugs: cholepoietic drugs [e.g., dehydrocholic acid, etc.], cholekinetic drugs [e.g., magnesium sulfate, etc.], etc.; central nervous system agonists: antianxiety drugs, hypnotic and sedative drugs, anesthetic drugs, spasmolytic drugs, autonomic drugs, anti-Parkinson drugs and other psychoneuro drugs, etc.; antitussive and expectorants [ephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate, isoproterenol hydrochloride,

ephedrine hydrochloride, methylephedrine hydrochloride, alloclamide, clofedanol, picoperidamine, cloperastine, protokylol, isoproterenol, salbutamol, terbutaline, oxymetebanol, morphine hydrochloride, dextromethorphan hydrobromide, oxycodone hydrochloride, dimemorfan phosphate, tipepidine hibenzate, pentoxyverine citrate, clofedanol hydrochloride, benzonatate, guaifenesin, bromhexine hydrochloride, ambroxol hydrochloride, acetylcysteine, ethylcysteine hydrochloride, carbocisteine, etc.], sedative drugs [chlorpromazine hydrochloride, atropine sulfate, phenobarbital, barbital, amobarbital, pentobarbital, thiopental sodium, thiamylal sodium, nitrazepam, estazolam, flurazepam, haloxazolam, triazolam, flunitrazepam, bromovalerylurea, chloral hydrate, triclofos sodium, etc.], analgesic and antiphlogistic drugs [e.g., central analgesic drugs (e.g., morphine, codeine, pentazocine etc.), steroidal drugs (e.g., prednisolone, dexamethasone, betamethasone, etc.), antiphlogistic enzymic drugs (e.g., bromelain, lysozymes, proctase, etc.)], diabetic drugs [sulfonylurea drugs (e.g., tolbutamide, chlorpropamide, glyclopyramide, acetohexamide, tolazamide, glibenclamide, glibuzole, etc.), biguanide drugs (e.g., metformin hydrochloride, buformin hydrochloride, etc.),

Please substitute the following paragraph for the second paragraph on page 122 of the specification.

Page 122, paragraph 2 (Currently Amended)

α-glucosidase inhibitors (e.g., voglibose, acarbose, etc.), insulin resistance improvers (e.g., pioglitazone, troglitazone, etc.), insulin, glucagon, diabetic complication drugs (e.g., epalrestat, thioctic acid, etc.), Actos, rosiglitazone, Kinedak, penfill, humulin, euglucon, glimicron, daonil, novolin, monotard, insulin family, glucobay, dimelin, rastinone, bacilcon, deamelin S, **Iszilin,** ~~**Iszlin acid,**~~ etc.]; brain function activating agents (e.g., idebenone, vinpocetine, etc.); urinary and male genital disease drugs [e.g., prostatomegaly drugs (tamsulosin

hydrochloride, prazosin hydrochloride, chlormadinone acetate, etc.), prostate cancer drugs (leuprorelin acetate, goserelin acetate, chlormadinone acetate, etc.)], etc; nonsteroidal antiinflammatory drugs [acetaminophen, phenacetin, ethenzamide, sulpyrine, antipyrine, migrenin, aspirin, mefenamic acid, fulfenamic acid, diclofenac sodium, loxoprofen sodium, phenylbutazone, indomethacin, ibuprofen, ketoprofen, naproxen, oxaprozin, flurbiprofen, fenbufen, pranoprofen, floctafenine, epirizole, tiaramide hydrochloride, zaltoprofen, gabexate mesilate, camostat mesilate, urinastatin, colchicine, probenecid, sulfinpyrazone, benzbromarone, allopurinol, sodium aurothiomalate, sodium hyaluronate, sodium salicylate, morphine hydrochloride, salicylic acid, atropine, scopolamine, morphine, pethidine, levorphanol, ketoprofen, naproxen, oxymorphone or salts thereof, etc.]; frequent urination and incontinence drugs [flavoxate hydrochloride, etc.]; unstable plaque stabilizers [MMP inhibitors, chymase inhibitors, etc.]; arrhythmic drugs [sodium channel blockers (e.g., quinidine, procainamide, disopyramide, ajmaline, cibenzoline, lidocaine, diphenylhydantoin, mexiletine, propafenone, flecainide, pilsicainide, phenytoin, etc.), β blockers (e.g., propranolol, alprenolol, bufetolol, oxprenolol, atenolol, acebutolol, metoprolol, ~~pisoprolol,~~ **bisoprolol,** pindolol, carteolol, arotinolol, etc.), potassium channel blockers (e.g., amiodarone, etc.), calcium channel blockers (e.g., verapamil, diltiazem, etc.), etc.];

Please substitute the following paragraph for the second paragraph on page 124 of the specification.

Page 124, paragraph 2 (Currently Amended)

gynecologic disease drugs [e.g., climacteric disorder drugs (conjugated estrogen, estradiol, testosterone enanthate, estradiol valerate, etc.), breast cancer drugs (tamoxifen citrate, etc.), endometriosis and hysteromyoma drugs (leuprorelin acetate, danazol, etc.)], etc.; anesthetic

drugs [a. local anaesthetic drugs [cocaine hydrochloride, procaine hydrochloride, lidocaine, dibucaine hydrochloride, tetracaine hydrochloride, mepivacaine hydrochloride, bupivacaine hydrochloride, oxybuprocaine hydrochloride, ethyl aminobenzoate, oxethazaine], etc.]; b. systemic anesthetic drugs [(1) inhalation anesthetic drugs (e.g., ether, halothane, nitrous oxide, influrane, enflurane), (2) intravenous anesthetic drugs (e.g., ketamine hydrochloride, droperidol, thiopental sodium, thiamylal sodium, pentobarbital), etc.]]; anesthetic antagonists [levallorphan, nalorphine, naloxone, or salts thereof, etc.]; chronic cardiac failure drugs: cardiac stimulants [e.g., cardiac glycoside (digoxin), etc., β receptor stimulants (catecholamine preparations such as denopamine, dobutamine), PDE inhibitors, etc.]; diuretic drugs [e.g., furosemide (Lasix), spironolactone (Aldactone), bumetanide (Lunetoron), azosemide (Diart), etc.]; ACE inhibitors [e.g., enalapril maleate (Renivace), etc.]; Ca antagonists [e.g., amlodipine, manidipine, etc.] and β receptor blockers, etc.; immunomodulators [cyclosporin, tacrolimus, gusperimus, azathioprine, antilymphocyte sera, dried sulfonated immunoglobulins, erythropoietins, growth promoting glycoproteins, interleukins, interferons, etc.]; diuretic drugs [thiazide-based diuretic drugs (benzylhydrochlorothiazide, cyclopenthiazide, ethiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, penfluthiazide, polythiazide, trichlormethiazide, etc.), loop diuretic drugs (chlortalidone, clofenamide, indapamide, mefruside, meticrane, ~~sotrazone, tribamide,~~ **tripamide,** quinethazone, metolazone, furosemide, mefruside, etc.), potassium-sparing diuretic drugs (spironolactone, triamterene, etc.)]; erectile dysfunction drugs (Viagra, apomorphine, etc.); and the like.

Please substitute the following paragraph for the first paragraph starting on page 223 of the specification.

Page 223, paragraph 1 (Currently Amended)

(Ss)-(2E)-3-[4'-(2-butoxyethoxy)-4-[3-(methoxycarbonyl)pyrrolidin-1-yl]-1,1'-biphenyl-3-yl]-2-methyl-N-[4-[[(1-propyl-1H-imidazol-5-yl)methyl]sulfinyl]phenyl]acrylamide (300 mg) was resolved by using ~~CHIRAKPAK~~ CHIRALPAK AD (50 mmID × 500 mmL) (hexane : 2-propanol = 1 : 1) to give two diastereomers [the former fraction: diastereomer 1 (Compound 57) (147 mg, >99%de) and the latter fraction: diastereomer 2 (Compound 58) (146 mg, >99%de)].

Please substitute the following paragraph for the second paragraph starting on page 359 of the specification.

Page 359, paragraph 2 (Currently Amended)

Reference Example 137

A suspension of methyl 1-[4-bromo-2-[(1E)-3-tert-butoxy-2-methyl-3-oxoprop-1-enyl]phenyl]pyrrolidine-3-carboxylate (550 mg), 4-(2-butoxyethoxy)phenylboric acid (402 mg) and potassium carbonate (466 mg) in toluene (15 ml), ethanol (1.5 ml) and water (1.5 ml) was stirred for 1 hour under an argon atmosphere. Then, tetrakis(triphenylphosphine)palladium (75 mg) was added thereto, and the resulting mixture was refluxed for 5 hours. After returning to room temperature, water was added thereto and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. The solvent was distilled off under reduced pressure, and then the resulting residue was purified by silica gel column chromatography (hexane : ethyl acetate = 18 : 1 → hexane : ethyl acetate = 4 : 1) to give ~~methyl 1-[4'-(2-butoxyethoxy)-3-[(1E)-3-tert-butoxy-2-methyl-3-oxoprop-1-enyl]-1'1-biphenyl-4-yl]pyrrolidine-3-carboxylate~~ methyl 1-[4'-(2-butoxyethoxy)-3-[(1E)-3-tert-

butoxy-2-methyl-3-oxoprop-1-enyl]-1,1'-biphenyl-4-yl]pyrrolidine-3-carboxylate (409 mg) as a yellow oily material.

Please substitute the following paragraph for the second paragraph starting on page 360 of the specification.

Page 360, paragraph 2 (Currently Amended)

Reference Example 138

Methyl ~~1-[4'-(2-butoxyethoxy)-3-[(1E)-3-tert-butoxy-2-methyl-3-oxoprop-1-enyl]-1'1-biphenyl-4-yl]pyrrolidine-3-carboxylate~~ **1-[4'-(2-butoxyethoxy)-3-[(1E)-3-tert-butoxy-2-methyl-3-oxoprop-1-enyl]-1,1'-biphenyl-4-yl]pyrrolidine-3-carboxylate** (400 mg) was dissolved in ethyl acetate (4 ml). Then, a 4 N hydrochloric acid-ethyl acetate solution (7 ml) was added thereto, and the mixture was stirred for 4 hours under a nitrogen atmosphere. Water was added thereto at 0°C and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After distilling off the solvent under reduced pressure, the resulting solids were washed with hexane to give (2E)-3-[4'-(2-butoxyethoxy)-4-[3-(methoxycarbonyl)pyrrolidin-1-yl]-1,1'-biphenyl-3-yl]-2-methylacrylic acid (273 mg) as yellow crystals.

m.p. 140.0-141.0°C.

Please substitute the following paragraph for the third paragraph starting on page 361 of the specification.

Page 361, paragraph 3 (Currently Amended)

Reference Example 139

To a solution of 1-benzyl-3,~~4dimethylpyrrolidine~~ **4-dimethylpyrrolidine** (9.0 g) in methanol (100 ml) and 1 N hydrochloric acid (48.9 ml) was added palladium carbon (10%, 4.5 g), and the mixture was stirred overnight under a hydrogen atmosphere. The insolubles were

removed by filtration, and then the solvent was distilled off under reduced pressure. Toluene was added thereto, and then the solvent was again distilled off under reduced pressure. The resulting residue was washed with hexane to give 3,4-dimethylpyrrolidine hydrochloride (5.93 g) as pale red crystals.